Chapter 7
The Role of Radiation Therapy

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Abbreviations

5-FU + LV	5-fluorouracil plus leucovorin
CMT	Chemotherapy
CRT	Chemoradiation
CT	Computerized tomography
DFS	Disease-free survival
Gy	Gray
HR	Hazard ratio
OR	Odds ratio
OS	Overall survival
RFS	Relapse-free survival
RT	Radiation therapy
XP	Capecitabine and cisplatin
XRT	Capecitabine with radiation therapy

Most patients with gastric cancer will have a locoregional failure after surgery alone [1]. The purpose of adjuvant RT is to achieve locoregional control that will ultimately translate into a survival benefit. In 2001, Macdonald et al. published the results of the Gastrointestinal Cancer Intergroup 0116 (INT 0116), setting CRT as the standard treatment of resected gastric cancer in Western countries [2].

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INT 0116

The INT 0116 randomized 556 patients to surgery alone or surgery plus adjuvant CRT. Adjuvant treatment consisted of a 5-day cycle of fluorouracil and leucovorin (5-FU + LV) followed by concurrent CRT starting on D28 (45 Gy in 25 fractions plus concurrent 5-FU + LV, 4 days/week at the beginning and at the end of radiation). After completing CRT, two additional 5-day cycles of 5-FU + LV were given at 1-month intervals. The trial demonstrated an overall survival (OS) benefit for the CRT group, with a median survival in the surgery-only group of 27 months versus 36 months in the CRT group. The HR for death was 1.35 (CI 95%, 1.09–1.66; $p = 0.005$). The RFS also favored the CRT group, with a median of 19 months versus 30 months; HR for relapse 1.52 (95% CI, 1.23–1.86; $p < 0.001$). The original publication had no data on histological subtypes.

A 10-year updated analysis was published in 2012 [3], and the benefit still persisted for the CRT in terms of OS with a HR of 1.32 (95% CI, 1.10–1.60; $p = 0.0046$) and for RFS with a HR of 1.51 (95% CI, 1.25–1.83; $p = 0.001$). The authors also reported an unplanned, exploratory subgroup analysis on the effect of therapy by selected patient characteristics. The results showed a trend for significant interaction in histology ($p = 0.077$), meaning that intestinal and diffuse subtypes could respond differently to CRT. The authors stated that in multivariate analysis, histology was significantly related to outcome, although no table of the multivariate analysis was given. A forest plot showed that intestinal subtype had a statistically significant benefit for OS, with a HR of approximately 1.4 (information extracted from figure); diffuse subtype had a HR of approximately 0.8, but with a confidence interval that crossed unity. The authors advise extreme caution in interpreting the results, given this was an unplanned, exploratory subanalysis and given the histologic subtype was known only in 77% of the patients (diffuse subtype accounted for 39% of the patients with known Lauren classification and 30% of the entire study).

An interesting finding of this study was that diffuse histology had better survival than intestinal histology. For example, in patients that received surgery alone, median survival was 42 months with diffuse histology versus 22 months with intestinal histology [3] (data supplement). These findings are in contrast to the general perception that diffuse-type gastric cancer carries a worse prognosis.

Although INT 0116 was a landmark trial, it was not globally accepted because of the limited lymph node dissection. Only 10% of the patients were submitted to a D2 dissection. There is debate on the benefit of a more extended lymph node dissection in gastric cancer. Some randomized studies failed to show benefit in extended dissection [4, 5], but more recent studies demonstrate better results in D2 dissection in locoregional recurrence and overall survival [6–8]. In Asia, there was a tendency to consider a D2 dissection sufficient for locoregional control.

ARTIST Trial

The ARTIST trial [9] was conducted in Korea to address the role of CRT in the setting of a D2 dissection. The trial compared adjuvant CMT versus CMT plus CRT. In the CMT arm, patients received six cycles of the XP regimen (capecitabine 1000 mg/m^2 twice daily on days 1–14; cisplatin 60 mg/m^2 on day 1 every 3 weeks). Patients assigned to the CRT arm received two cycles of XP (capecitabine 1000 mg/m^2 twice daily on days 1–14; cisplatin 60 mg/m^2 on day 1 every 3 weeks), then XRT (45 Gy at 1.8 Gy per day, 5 days per week, for 5 weeks with continuous capecitabine 825 mg/m^2 twice daily during radiotherapy), followed by two additional cycles of XP (capecitabine 1000 mg/m^2 twice daily on days 1–14; cisplatin 60 mg/m^2 on day 1 every 3 weeks). The primary endpoint was disease-free survival (DFS). For this trial, 458 patients were recruited, with 60% of patients having diffuse-subtype histology. In their first publication in 2012, the authors showed a non statistically significant difference in DFS favoring CRT. In subgroup analysis, the benefit of the CRT was statistically significant for patients with positive lymph nodes ($p = 0.035$), with a HR for DFS of 0.68 (95% CI 0.47–0.99). The authors subsequently published an update in 2015 [10] showing that there was significant interaction of both lymph node status and Lauren classification with treatment. The results demonstrated that the addition of RT to adjuvant CMT in the positive lymph node or intestinal-type subgroups significantly improved outcome.

At this point, we point out potential limitations in the sample size calculation of the ARTIST trial: The INT 0116 and the Magic trial [11] compared CRT and CMT with no adjuvant treatment. Each accrued close to 500 patients, and the HR for DFS was 1.5 in both trials. The ARTIST trial based its sample size calculation on a HR of 1.45 and recruited 458 patients. We would argue that to detect a difference in DFS between two active treatments, one should estimate a more modest HR and recruit close to twice as many patients. In addition, the ARTIST trial recruited 60% of early-stage disease patients (IB-II), resulting in fewer events (relapse or death) than was originally planned. These highlight that the overall results of the trial that demonstrated a lack of benefit of CRT in the context of adjuvant CMT could be due to a type-2 error (insufficient power to detect a difference between treatment arms).

One should also interpret with caution the results of the subgroup analyses in the INT 0116 and ARTIST trial. The positive interaction between Lauren classification and treatment suggests that intestinal and diffuse subtypes respond differently to treatment. This is different than stating that the diffuse subtype does not respond to treatment. This is illustrated by the data from the CROSS trial, which compared neoadjuvant CRT plus surgery to surgery alone in esophageal cancer [12]. The original publication showed a survival benefit favoring the CRT arm. In subgroup analysis, the benefit was statistically significant in squamous cell carcinoma (SCC) but not in adenocarcinoma. Some suggested that the results of the trial were only applicable to SCC. However, longer follow-up [13] showed that both SCC and adenocarcinoma had a statistically significant benefit with treatment, with a bigger magnitude of effect in SCC. Therefore, we advise extreme caution in the interpretation of data from subgroup analysis.

SEER Data

Stessin et al. [14] retrospectively analyzed the Surveillance, Epidemiology, and End Results (SEER) database looking at the role of adjuvant RT in the setting of diffuse gastric cancer. The authors included patients treated between 2002 and 2005 (after the publication of the INT 0116 in 2001 and before the publication of the MAGIC trial in 2006), when the expected adjuvant treatment would be CRT. They identified a total of 1889 patients with diffuse-type gastric cancer that underwent surgery and had no distant metastasis, of whom 782 received adjuvant RT and 1107 did not. Using a propensity score matching strategy, the results showed a survival benefit favoring RT, with a median survival of 30 months in the group treated with adjuvant RT versus 18 months in the group that did not receive RT ($p < 0.001$). Multivariate Cox proportional hazards regression analysis demonstrated that the addition of adjuvant RT was associated with better survival, with a HR of 0.75 (95% CI, 0.65–0.82; $p < 0.001$). Aside from the inherent limitations of the retrospective design, one important confounder was that data from CMT could not be retrieved from the SEER database. Patients in the no RT arm could have received adjuvant or perioperative CMT, despite not being standard treatment during the inclusion period. However, if a proportion of patients in the control arm did receive CMT, the results would be biased toward reducing the magnitude of benefit of RT, thus confirming that the results of this analysis are robust.

Table 7.1 summarizes selected results of studies that report the rate of diffuse subtype histology in gastric cancer.

Table 7.1 Selected results of RT in gastric cancer

Study	Type	Comparison (first standard arm)	N of Pts	Percentage diffuse(%)	OS	*p*-value
INT0116 (2001)	Prospective randomized	Observation vs. adjuvant CRT	556	30	Median 27 m vs. 36 m	0.005
ARTIST (2011)	Prospective randomized	Adjuvant CMT vs. CRT	458	60	5-year 73% vs. 75%	0.484
SEER (2014)	Retrospective propensity score	Adjuvant (C)RT vs. observation	1889	100	Median 30 m vs. 18 m	<0.001

N of Pts number of patients, *OS* overall survival, *CRT* chemoradiotherapy, *CMT* chemotherapy, *m* months

Meta-analysis

A Chinese meta-analysis published in 2014 [15], including 6 randomized trials comparing adjuvant CRT versus adjuvant CMT, showed that adjuvant CRT could significantly improve the 5-year DFS rate (OR 1.56, 95% CI: 1.09–2.24) and reduce the locoregional recurrence rate (OR 0.46, 95% CI: 0.32–0.67) compared with CMT, but there was no difference in 5-year OS rates (OR 1.32, 95% CI: 0.92–1.88). The authors did not have a formal statistical analysis according to histology, but almost 56% of the patients had diffuse subtype.

Patterns of Relapse

Marelli et al. conducted a multicenter longitudinal study to evaluate patterns of relapse in patients subjected to potentially curative surgery for gastric cancer with no adjuvant treatment [16]. The incidence of locoregional, hematogenous, and peritoneal recurrence were respectively 27%, 16%, and 34% in the diffuse subtype and 20%, 19%, and 9% in the intestinal subtype, respectively.

In our experience at Instituto do Câncer do Estado de São Paulo (ICESP), we retrospectively reviewed 104 patients treated with adjuvant CRT in gastric cancer [17], according to the INT0116 scheme. Most of the patients had advanced locoregional disease, with 85% having T3 or T4 tumors, 82% having positive nodes, and 42% having diffuse-type histology. The median survival was 38.3 months in intestinal subtype versus *not reached* in the diffuse subtype ($p = 0.48$). In univariate and multivariate analysis, histology was not correlated with differences in DFS or OS. Patterns of relapse were also not different, with locoregional, peritoneal, and systemic relapses of respectively 9%, 10%, and 11% for the diffuse subtype and 10%, 13%, and 13% for the intestinal subtype (p = NS).

The INT 0116 and ARTIST trials both showed a reduction in locoregional recurrence with CRT [3, 9], but they did not publish patterns of recurrence according to histology.

Ongoing Trials

There are currently three prospective randomized phase III trials addressing the role of RT in different scenarios of gastric cancer. All of them include both intestinal and diffuse subtypes.

The ARTIST II trial (NCT01761461) will compare adjuvant CMT versus CRT in patients with positive lymph nodes after gastrectomy plus D2 dissection. Randomization will be stratified based on histology [18].

The CRITICS trial (NCT00407186) will compare perioperative CMT with epirubicin, cisplatin, and capecitabine versus the same neoadjuvant CMT plus adjuvant CRT (45 Gy with five fractions with weekly cisplatin and daily capecitabine) in patients with gastric cancer. Randomization was stratified by histology. This trial has completed recruitment. At the initial analysis [19], OS was similar between the two groups, with a 5-year survival of 41.3% for CMT and 40.9% for CRT ($p = 0.99$). The toxicity profile was similar, except for neutropenia, where the CRT group had statistically significantly fewer events (hematological grade III or higher: 44% vs. 34%; $p = 0.01$). No subgroup analyses have been presented so far.

The TOPGEAR trial (NCT01924819) will compare preoperative CRT versus preoperative CMT for resectable gastric and gastroesophageal junction cancer. The randomization will be based on a minimization process, but patients will not be stratified by histology [20].

To the extent of our knowledge, there are no published or ongoing phase III trials addressing the role of radiation therapy specifically in diffuse-type-only gastric cancer. We acknowledge that this issue is highly controversial and that ultimately only a well-designed randomized phase III trial may settle the debate. Until then, based on the currently available data, we recommend adjuvant CRT to all patients with T2 to T4 or N+ resected gastric cancer, irrespective of histology.

Radiation Therapy Recommendations

Indications for adjuvant treatment with CRT: T2–T4 or N+.

Dose 45 Gy in 25 fractions of 1.8Gy per day, 5 fractions per week. An additional dose may be performed if margins are positive with 5.4Gy in 3 fractions of 1.8Gy per day.

Simulation Fast for 4 h before simulation computerized tomography (CT). Simulate in supine position with arms up and above the head.

Accessories Wing board or vac-fix.

Use 4D-CT to account for diaphragm motion.

Volumes of treatment Always include tumor bed, anastomosis, remaining stomach, and perigastric lymph nodes. Other locations and lymph node chains depend on primary site, T and N stage, and type of dissection.

Lymph node chains at risk according to primary site [21]:

- Gastroesophageal junction: periesophageal, mediastinal, and celiac
- Cardia and proximal: periesophageal, mediastinal, celiac, splenic, and suprapancreatic
- Body: celiac, splenic, suprapancreatic, pancreaticoduodenal, and porta hepatis

– Antrum, pylorus, and distal: celiac, suprapancreatic, pancreaticoduodenal, porta hepatis

Organs at risk Heart, lungs, liver, kidneys, and spinal cord.

Technique 3D conformal or intensity-modulated radiation therapy (IMRT); IMRT can be used to spare heart, lungs, and kidneys if organs-at-risk constraints cannot be met with 3D conformal RT. Apparently there is no difference in disease control and treatment toxicity [22, 23]. IMRT may reduce late nephrotoxicity [24].

Weekly patient evaluation during treatment looking at toxicity and early introduction of symptomatics.

Acute toxicities Fatigue, nausea, anorexia, myelosuppression (due to concomitant CMT), dyspepsia, gastritis, and ulcer.

Commonly used medicines Antiemetics as dimenhydrinate, metoclopramide or ondansetron given 1 h before treatment.

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